

WHAT IS CLAIMED IS:

1. A method for ameliorating the harmful effects of TNF in an animal, comprising administering to an animal in need of such treatment a therapeutically effective amount of a recombinant polypeptide having the ability to bind TNF, wherein  
5 said polypeptide is encoded by a nucleic acid molecule comprising a nucleotide sequence of the formula:  $R^1-R^2-R^3-R^4$ , wherein

$R^1$  is ATG, or the nucleotide sequence ATG GGC CTC TCC ACC GTG CCT GAC CTG CTG CTG CCA CTG GTG CTC CTG GAG CTG TTG GTG GGA ATA  
10 TAC CCC TCA GGG GTT ATT GGA (SEQ ID NO: 5), or is absent;

$R^2$  is the nucleotide sequence CTG GTC CCT CAC CTA GGG GAC AGG GAG AAG AGA (SEQ ID NO: 7) or is absent;

$R^3$  is the nucleotide sequence of SEQ ID NO: 3; and

$R^4$  is the nucleotide sequence GTT AAG GGC ACT GAG GAC TCA GGC ACC  
15 ACA (SEQ ID NO: 9) or is absent.

2. The method of Claim 1, wherein  $R^1$  is ATG,  $R^2$  is the nucleotide sequence CTG GTC CCT CAC CTA GGG GAC AGG GAG AAG AGA (SEQ ID NO: 7), and  $R^4$  is the nucleotide sequence GTT AAG GGC ACT GAG GAC TCA GGC ACC ACA  
20 (SEQ ID NO: 9).

3. The method of Claim 1, wherein  $R^1$  is ATG,  $R^2$  is the nucleotide sequence CTG GTC CCT CAC CTA GGG GAC AGG GAG AAG AGA (SEQ ID NO: 7), and  $R^4$  is absent.  
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4. The method of Claim 1, wherein  $R^1$  is ATG,  $R^2$  is absent, and  $R^4$  is the nucleotide sequence GTT AAG GGC ACT GAG GAC TCA GGC ACC ACA (SEQ ID NO: 9).

30 5. The method of Claim 1, wherein  $R^1$  is ATG,  $R^2$  is absent, and  $R^4$  is absent.

6. The method of Claim 1, wherein R<sup>1</sup> is the nucleotide sequence ATG GGC CTC TCC ACC GTG CCT GAC CTG CTG CTG CCA CTG GTG CTC CTG GAG CTG TTG GTG GGA ATA TAC CCC TCA GGG GTT ATT GGA (SEQ ID NO: 5), R<sup>2</sup> is the nucleotide sequence CTG GTC CCT CAC CTA GGG GAC AGG GAG AAG AGA (SEQ ID NO: 7), and R<sup>4</sup> is the nucleotide sequence GTT AAG GGC ACT GAG GAC TCA GGC ACC ACA (SEQ ID NO: 9).

7. The method of Claim 1, wherein R<sup>1</sup> is the nucleotide sequence ATG GGC CTC TCC ACC GTG CCT GAC CTG CTG CTG CCA CTG GTG CTC CTG GAG CTG TTG GTG GGA ATA TAC CCC TCA GGG GTT ATT GGA (SEQ ID NO: 5), R<sup>2</sup> is the nucleotide sequence CTG GTC CCT CAC CTA GGG GAC AGG GAG AAG AGA (SEQ ID NO: 7), and R<sup>4</sup> is absent.

8. The method of Claim 1, wherein R<sup>1</sup> is the nucleotide sequence ATG GGC CTC TCC ACC GTG CCT GAC CTG CTG CTG CCA CTG GTG CTC CTG GAG CTG TTG GTG GGA ATA TAC CCC TCA GGG GTT ATT GGA (SEQ ID NO: 5), R<sup>2</sup> is absent, and R<sup>4</sup> is the nucleotide sequence GTT AAG GGC ACT GAG GAC TCA GGC ACC ACA (SEQ ID NO: 9).

9. The method of Claim 1, wherein R<sup>1</sup> is the nucleotide sequence ATG GGC CTC TCC ACC GTG CCT GAC CTG CTG CTG CCA CTG GTG CTC CTG GAG CTG TTG GTG GGA ATA TAC CCC TCA GGG GTT ATT GGA (SEQ ID NO: 5), R<sup>2</sup> is absent, and R<sup>4</sup> is absent.

10. The method of Claim 1, wherein R<sup>1</sup> is absent, R<sup>2</sup> is the nucleotide sequence CTG GTC CCT CAC CTA GGG GAC AGG GAG AAG AGA (SEQ ID NO: 7), and R<sup>4</sup> is the nucleotide sequence GTT AAG GGC ACT GAG GAC TCA GGC ACC ACA (SEQ ID NO: 9).

11. The method of Claim 1, wherein  $R^1$  is absent,  $R^2$  is the nucleotide sequence CTG GTC CCT CAC CTA GGG GAC AGG GAG AAG AGA (SEQ ID NO: 7), and  $R^4$  is absent.

5 12. The method of Claim 1, wherein  $R^1$  is absent,  $R^2$  is absent, and  $R^4$  is the nucleotide sequence GTT AAG GGC ACT GAG GAC TCA GGC ACC ACA (SEQ ID NO: 9).

10 13. The method of Claim 1, wherein  $R^1$  is absent,  $R^2$  is absent, and  $R^4$  is absent.

14. A method for ameliorating the harmful effects of TNF in an animal, comprising administering to an animal in need of such treatment a therapeutically effective amount of a recombinant polypeptide having the ability to bind TNF, wherein  
15 said polypeptide is encoded by a nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO: 1.

15. A method for ameliorating the harmful effects of TNF in an animal, comprising administering to an animal in need of such treatment a therapeutically effective amount of a recombinant polypeptide having the ability to bind TNF, wherein  
20 said polypeptide comprises an amino acid sequence of the formula:  $R^1$ - $R^2$ - $R^3$ - $R^4$ , wherein

$R^1$  is methionine, or the amino acid sequence Met Gly Leu Ser Thr Val Pro Asp Leu Leu Leu Pro Leu Val Leu Leu Glu Leu Leu Val Gly Ile Tyr Pro Ser Gly Val Ile Gly  
25 (SEQ ID NO: 6), or is absent;

$R^2$  is the amino acid sequence Leu Val Pro His Leu Gly Asp Arg Glu Lys Arg (SEQ ID NO: 8) or is absent;

$R^3$  is the amino acid sequence of SEQ ID NO: 4; and

$R^4$  is the amino acid sequence Val Lys Gly Thr Glu Asp Ser Gly Thr Thr (SEQ  
30 ID NO: 10) or is absent; and

wherein said polypeptide has:

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- a) at least one conservative amino acid substitution;
  - b) at least one amino acid substitution at a glycosylation site;
  - c) at least one amino acid substitution at a proteolytic cleavage site;
  - d) at least one amino acid substitution at a cysteine residue;
  - e) at least one amino acid deletion;
  - f) at least one amino acid insertion;
  - g) a C- and/or N-terminal truncation; or
  - h) a combination of modifications selected from the group consisting of conservative amino acid substitutions, amino acid substitutions at a glycosylation site,
- 10 amino acid substitutions at a proteolytic cleavage site, amino acid substitutions at a cysteine residue, amino acid deletions, amino acid insertions, C-terminal truncation, and N-terminal truncation.

15 16. The method of Claim 15, wherein said polypeptide comprises an amino acid sequence of the formula:  $R^1-R^2-R^3-R^4$  and has at least one conservative amino acid substitution.

20 17. The method of Claim 15, wherein said polypeptide comprises an amino acid sequence of the formula:  $R^1-R^2-R^3-R^4$  and has at least one amino acid substitution at a glycosylation site.

25 18. The method of Claim 15, wherein said polypeptide comprises an amino acid sequence of the formula:  $R^1-R^2-R^3-R^4$  and has at least one amino acid substitution at a proteolytic cleavage site.

19. The method of Claim 15, wherein said polypeptide comprises an amino acid sequence of the formula:  $R^1-R^2-R^3-R^4$  and has at least one amino acid substitution at a cysteine residue.

30 20. The method of Claim 15, wherein said polypeptide comprises an amino acid sequence of the formula:  $R^1-R^2-R^3-R^4$  and has at least one amino acid deletion.

21. The method of Claim 15, wherein said polypeptide comprises an amino acid sequence of the formula:  $R^1-R^2-R^3-R^4$  and has at least one amino acid insertion.

22. The method of Claim 15, wherein said polypeptide comprises an amino acid sequence of the formula:  $R^1-R^2-R^3-R^4$  and has a C- and/or N-terminal truncation.

23. A method for ameliorating the harmful effects of TNF in an animal, comprising administering to an animal in need of such treatment a therapeutically effective amount of a recombinant polypeptide having the ability to bind TNF, wherein said polypeptide comprises an amino acid sequence of the formula:  $R^1-R^2-R^3-R^4$ , wherein

$R^1$  is methionine, or the amino acid sequence Met Gly Leu Ser Thr Val Pro Asp Leu Leu Leu Pro Leu Val Leu Leu Glu Leu Leu Val Gly Ile Tyr Pro Ser Gly Val Ile Gly (SEQ ID NO: 6), or is absent;

$R^2$  is the amino acid sequence Leu Val Pro His Leu Gly Asp Arg Glu Lys Arg (SEQ ID NO: 8) or is absent;

$R^3$  is the amino acid sequence of SEQ ID NO: 4; and

$R^4$  is the amino acid sequence Val Lys Gly Thr Glu Asp Ser Gly Thr Thr (SEQ ID NO: 10) or is absent.

24. The method of Claim 23, wherein  $R^1$  is methionine,  $R^2$  is the amino acid sequence Leu Val Pro His Leu Gly Asp Arg Glu Lys Arg (SEQ ID NO: 8), and  $R^4$  is the amino acid sequence Val Lys Gly Thr Glu Asp Ser Gly Thr Thr (SEQ ID NO: 10).

25. The method of Claim 23, wherein  $R^1$  is methionine,  $R^2$  is the amino acid sequence Leu Val Pro His Leu Gly Asp Arg Glu Lys Arg (SEQ ID NO: 8), and  $R^4$  is absent.

26. The method of Claim 23, wherein  $R^1$  is methionine,  $R^2$  is absent, and  $R^4$  is the amino acid sequence Val Lys Gly Thr Glu Asp Ser Gly Thr Thr (SEQ ID NO: 10).

27. The method of Claim 23, wherein R<sup>1</sup> is methionine, R<sup>2</sup> is absent, and R<sup>4</sup> is absent.

28. The method of Claim 23, wherein R<sup>1</sup> is the amino acid sequence Met Gly Leu Ser Thr Val Pro Asp Leu Leu Leu Pro Leu Val Leu Leu Glu Leu Leu Val Gly Ile Tyr Pro Ser Gly Val Ile Gly (SEQ ID NO: 6), R<sup>2</sup> is the amino acid sequence Leu Val Pro His Leu Gly Asp Arg Glu Lys Arg (SEQ ID NO: 8), and R<sup>4</sup> is the amino acid sequence Val Lys Gly Thr Glu Asp Ser Gly Thr Thr (SEQ ID NO: 10).

29. The method of Claim 23, wherein R<sup>1</sup> is the amino acid sequence Met Gly Leu Ser Thr Val Pro Asp Leu Leu Leu Pro Leu Val Leu Leu Glu Leu Leu Val Gly Ile Tyr Pro Ser Gly Val Ile Gly (SEQ ID NO: 6), R<sup>2</sup> is the amino acid sequence Leu Val Pro His Leu Gly Asp Arg Glu Lys Arg (SEQ ID NO: 8), and R<sup>4</sup> is absent.

30. The method of Claim 23, wherein R<sup>1</sup> is the amino acid sequence Met Gly Leu Ser Thr Val Pro Asp Leu Leu Leu Pro Leu Val Leu Leu Glu Leu Leu Val Gly Ile Tyr Pro Ser Gly Val Ile Gly (SEQ ID NO: 6), R<sup>2</sup> is absent, and R<sup>4</sup> is the amino acid sequence Val Lys Gly Thr Glu Asp Ser Gly Thr Thr (SEQ ID NO: 10).

31. The method of Claim 23, wherein R<sup>1</sup> is the amino acid sequence Met Gly Leu Ser Thr Val Pro Asp Leu Leu Leu Pro Leu Val Leu Leu Glu Leu Leu Val Gly Ile Tyr Pro Ser Gly Val Ile Gly (SEQ ID NO: 6), R<sup>2</sup> is absent, and R<sup>4</sup> is absent.

32. The method of Claim 23, wherein R<sup>1</sup> is absent, R<sup>2</sup> is the amino acid sequence Leu Val Pro His Leu Gly Asp Arg Glu Lys Arg (SEQ ID NO: 8), and R<sup>4</sup> is the amino acid sequence Val Lys Gly Thr Glu Asp Ser Gly Thr Thr (SEQ ID NO: 10).

33. The method of Claim 23, wherein R<sup>1</sup> is absent, R<sup>2</sup> is the amino acid sequence Leu Val Pro His Leu Gly Asp Arg Glu Lys Arg (SEQ ID NO: 8), and R<sup>4</sup> is absent.

34. The method of Claim 23, wherein R<sup>1</sup> is absent, R<sup>2</sup> is absent, and R<sup>4</sup> is the amino acid sequence Val Lys Gly Thr Glu Asp Ser Gly Thr Thr (SEQ ID NO: 10).

5           35. The method of Claim 23, wherein R<sup>1</sup> is absent, R<sup>2</sup> is absent, and R<sup>4</sup> is absent.

36. A method for ameliorating the harmful effects of TNF in an animal, comprising administering to an animal in need of such treatment a therapeutically  
10 effective amount of a recombinant polypeptide having the ability to bind TNF, wherein said polypeptide comprises the amino acid sequence of SEQ ID NO: 2.

37. A method for ameliorating the harmful effects of TNF in an animal, comprising administering to an animal in need of such treatment a therapeutically  
15 effective amount of a recombinant polypeptide having the ability to bind TNF, wherein said polypeptide comprises the amino acid sequence of SEQ ID NO: 4 or a C- and/or N-terminally shortened sequence thereof.

38. The method of Claim 37, wherein said polypeptide further comprises an  
20 amino-terminal methionine.

39. The method of Claim 37, wherein said polypeptide comprises a C-terminally shortened sequence of the amino acid sequence of SEQ ID NO: 4.

25           40. The method of Claim 39, wherein said polypeptide further comprises an amino-terminal methionine.

41. A method for ameliorating the harmful effects of TNF in an animal, comprising administering to an animal in need of such treatment a therapeutically  
30 effective amount of a recombinant polypeptide having the ability to bind TNF, wherein said polypeptide consists of the amino acid sequence of SEQ ID NO: 4.

42. A method for ameliorating the harmful effects of TNF in an animal, comprising administering to an animal in need of such treatment a therapeutically effective amount of a recombinant polypeptide having the ability to bind TNF, wherein  
5 said polypeptide is nonglycosylated or is glycosylated by a CHO cell, and wherein said polypeptide consists of the amino acid sequence of SEQ ID NO: 4 and an amino-terminal methionine.

43. A method for ameliorating the harmful effects of TNF in an animal,  
10 comprising administering to an animal in need of such treatment a therapeutically effective amount of a recombinant polypeptide having the ability to bind TNF, wherein said polypeptide consists of a C-terminally shortened sequence of the amino acid sequence of SEQ ID NO: 4.

44. A method for ameliorating the harmful effects of TNF in an animal,  
15 comprising administering to an animal in need of such treatment a therapeutically effective amount of a recombinant polypeptide having the ability to bind TNF, wherein said polypeptide consists of a C-terminally shortened sequence of the amino acid sequence of SEQ ID NO: 4 and an amino-terminal methionine.

20 45. The method of either Claims 15 or 34, wherein said polypeptide has at least one additional amino acid at the amino-terminus, at the carboxyl-terminus, or at both the amino-terminus and the carboxyl-terminus.

25 46. The method of Claim 45, wherein said polypeptide has at least one additional amino acid at the amino-terminus.

47. The method of Claim 46, wherein said polypeptide has a methionine at the  
30 amino-terminus.



48. The method of Claim 45, wherein said polypeptide has at least one additional amino acid at the carboxyl-terminus.

49. A method for ameliorating the harmful effects of TNF in an animal, comprising administering to an animal in need of such treatment a therapeutically effective amount of a recombinant polypeptide having the ability to bind TNF, wherein said polypeptide is encoded by a nucleic acid which hybridizes under moderately or highly stringent conditions to the complement of the nucleic acid molecule defined in Claim 1.

50. The method of any of Claims 1, 15, or 23, wherein said polypeptide is chemically derivatized.

51. The polypeptide of any of Claims 1, 14, 15, 23, 36, 37, 41, 42, 43, 44, or 49, wherein said polypeptide is not glycosylated.

52. The polypeptide of any of Claims 1, 14, 15, 23, 36, 37, 41, 42, 43, 44, or 49, wherein said polypeptide is glycosylated.

53. The polypeptide of Claim 52, wherein said polypeptide is glycosylated by a CHO cell.

54. The method of any of Claims 1, 15, or 23, wherein said recombinant polypeptide is expressed in a cultured cell *in vitro* and said recombinant polypeptide is isolated therefrom.

55. The method of Claim 54, wherein the cultured cell is a non-human cell.

56. The method of Claim 55, wherein the non-human cell line is a prokaryotic cell.

57. The method of Claim 56, wherein the prokaryotic cell is *Escherichia coli*.

58. The method of Claim 55, wherein the non-human cell line is a eukaryotic cell.

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59. The method of Claim 58, wherein the eukaryotic cell is a mammalian cell.

60. The method of Claim 59, wherein the mammalian cell is a Chinese Hamster Ovary cell or a COS cell.

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61. The method of Claim 54, wherein the polypeptide is glycosylated.

62. The method of Claim 54, wherein the polypeptide is not glycosylated.

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